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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,495	01/26/2007	Hisatoshi Shida	1254-0315PUS1	3821

2292 7590 12/09/2008

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EXAMINER	
MOSHER, MARY	
ART UNIT	**PAPER NUMBER**
1648	

NOTIFICATION DATE	DELIVERY MODE
12/09/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/581,495	SHIDA ET AL.	
	Examiner	Art Unit	
	Mary E. Mosher	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *8-10 and 19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,11-18 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/6/06, 6/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group I, claims 1-7 and 11-18 in the reply filed on 8/18/2008 is acknowledged.

Claims 8-10, 19-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/18/2008.

On reconsideration, claims 22-24 are rejoined with group I, because of the amendment to these claims.

Claim Rejections - 35 USC § 112

Claims 1-7, 11-18, 22-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is confusing, in that it is not clear if it is directed to a virus per se or a vaccine composition. It is also not clear if the claim is limited to viruses of strains LC16, LC16m0, and LC16m8, or if the claim is drawn to any vaccinia strain which has a B5R gene from one of these strains. Claim 12 has similar problems. In addition, it is not clear if claims 11 and 24 are drawn to a pharmaceutical composition or a vaccine; these are different in scope. In addition, should claim 17 depend from claim 14 instead of claim 12?

In the interest of compact prosecution, claim 1 has been treated as if it were drawn to a vaccinia virus variant of strain LC16, LC16m0, or LC16m8, which has a B5R mutation that does not easily undergo reverse mutation, and which produces no B5R

gene products having normal functions. Claim 12 has been treated as drawn to a vaccinia virus vector with the same limitations as claim 1. However, this treatment does not relieve applicant of the burden of response to this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 11-13, 15, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Engelstad et al (Virology 194:627-637, 1993). If the claims are not meant to be limited to strains LC16, LC16m0, and LC16m8, then the following rejection applies. Engelstad teaches a vaccinia virus which is deficient in the whole of the B5R gene, by virtue of deletion of the entire gene. If the LC16 strain B5R gene were transferred into strain WR or IHD-J, then deleted, the resulting virus would be identical to the deletion mutants described in the publication. The reference mutants make small plaques, like LC16m8, and could be used as vectors. Therefore, if the claims are not meant to be limited to strains LC16, LC16m0, and LC16m8, the reference appears to meet each and every limitation of these claims.

Allowable Subject Matter

Claims 1-7, 11-18, 22-24 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action.

The following is a statement of reasons for the indication of allowable subject matter: The LC16, LC16m8, and LC16m0 strains are closely related to each other, and were well known in the prior art. The LC16m8 strain is a more-highly-attenuated variant of the other two strains, and it was used for extensive human vaccination in Japan in the 1970's. The functions of the B5R gene were also known in the prior art, and are discussed in detail on specification pages 12-13.

It was known in the art that deletion of the B5R gene caused severe attenuation in vaccinia, see for example Engelstad et al (Virology 194:627-637, 1993). It also was known in the art that the B5R gene in LC16m8 had a single nucleotide frameshift mutation that was responsible for plaque size and host range phenotype of the strain, see Takahashi-Nishimaki et al (Virology 181:158-164, 1991). The mutation caused premature termination of the protein. Sugimoto et al (Vaccine 12:675-681, 1994) reviews the LC16m8 strain, and states that “The genes responsible for neurovirulence and temperature sensitivity do not seem to correlate with the B5R gene, and remain to be identified.” Sugimoto also indicates concern regarding over-attenuation leading to poor immunogenicity with further manipulation of LC16m0 vectors, see page 680. Jacobs (WO 2004/087047, not prior art) reiterates these same concerns, see page 3. Smith et al (Journal of General Virology 83:2915-2931, 2002) also state the concern on page 2925: "Given that B5R is the only established target for EEV neutralizing antibody, [LC16m8] might have diminished potency as a smallpox vaccine.” Cohen (Science 298:2314, 2002) also indicates that “some leading poxvirus researchers have serious reservations about LC16m8 because it doesn’t go through the stage in the viral

life cycle called extracellular enveloped virus, which produces the main protective antibody response in vaccinia." On the other hand, Sugimoto et al 2003 (in IDS) cite unpublished results that indicate "the protective capacity of LC16m8 was found to differ little from that of its parent strain, i.e. the conventional LO strain."

Katz et al (AIDS Research and Human retroviruses 13:1497-1500, 1997) teach an immunogenic vaccinia virus with HIV envelope protein sequence fused to the C-terminal region of B5R; however, the process used to construct the virus of Katz did not remove or alter the wild-type B5R in the vaccinia genome.

To summarize: the functions of the B5R gene in vaccinia virus were known, including its presence in extracellular enveloped virus and its role as a major protective antigen. Deletion of the B5R gene was known to severely attenuate vaccinia. It was known that a frameshift mutation in the B5R gene was present in strain LC16m8, and there was widespread concern that LC16m8 might be over-attenuated. Contrasting with the widespread concern was a single sentence mentioning an unpublished study. Viewing the prior art as a whole, in the absence of hindsight there was no particular reason to modify the B5R gene of strains LC16, LC16m8, or LC16m0 to render the B5R gene nonfunctional by a mutation that could not be easily reverted, and there was not a reasonable expectation of success for obtaining an effective anti-poxvirus immune response using such a nonreverting mutant. Applicants have shown that B5R in LC16m8 undergoes spontaneous reversion, and that the claimed variants do not. This may be obvious in hindsight; however, the prior art failed to indicate concern over possible reversion of the frameshift mutation in LC16m8. Furthermore, applicants have

shown that the claimed viruses are not over-attenuated; in an animal challenge model, the claimed viruses showed equal protection against vaccinia compared to known effective vaccine strains. See Example 6 in the specification.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is 571-272-0906. The examiner can normally be reached on varying dates and times; please leave a message.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mary E Mosher/
Primary Examiner, Art Unit 1648

12/4/08